



PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07C 209/52	A1	(11) International Publication Number: WO 99/47486 (43) International Publication Date: 23 September 1999 (23.09.99)
<p>(21) International Application Number: PCT/EP99/01696</p> <p>(22) International Filing Date: 16 March 1999 (16.03.99)</p> <p>(30) Priority Data: 645/98 18 March 1998 (18.03.98) CH</p> <p>(71) Applicant (for all designated States except US): CIBA SPECIALTY CHEMICALS HOLDING INC. [CH/CH]; Klybeckstrasse 141, CH-4057 Basle (CH).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): STEINER, Heinz [CH/CH]; Dahlienstrasse 28, CH-4416 Bubendorf (CH). BENZ, Markus [CH/CH]; Baselstrasse 16, CH-4144 Arlesheim (CH). JALETT, Hans-Peter [CH/CH]; Solothurnerstrasse 2, CH-4143 Dornach (CH). THOMMEN, Marc [CH/CH]; Ausserdorfstrasse 10, CH-4412 Nuglar (CH).</p> <p>(74) Agent: CIBA SPECIALTY CHEMICALS HOLDING INC.; Patentabteilung, Klybeckstrasse 141, CH-4057 Basel (CH).</p>		<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: PROCESS FOR THE CIS-SELECTIVE CATALYTIC HYDROGENATION OF CYCLOHEXYLIDENAMINES</p> <p>(57) Abstract</p> <p>This invention relates to a process for the cis-selective preparation of cyclic amines of the sertraline type by reductive alkylation of cyclic immines or of their precursors and for the catalytic hydrogenation in the presence of copper-containing catalysts.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

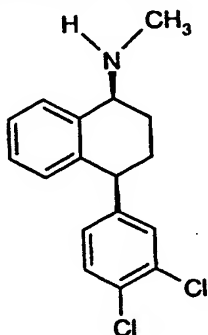
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

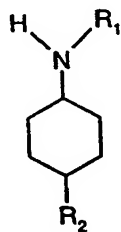
Process for the cis-selective catalytic hydrogenation of cyclohexylidenamines

The present invention relates to a novel, inventive process for the cis-selective catalytic hydrogenation of cyclohexylidenamines and their precursors.

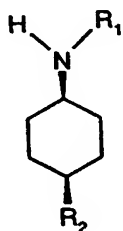
Cyclohexylamines can be used, inter alia, as antioxidants and as pharmaceutical active substances. An important cyclohexylamine is sertraline:



Sertraline: (1S,4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthylamine, see *Merck Index Twelfth Edition 1996, No. 8612*, is known as antidepressant. The preparation of this compound is described in *U.S. patent specification No. 4,536,518*. The hydrochloride is commercially available, inter alia under the registered trademarks Lustral® and Zoloft®. The cyclohexylamines of the type:

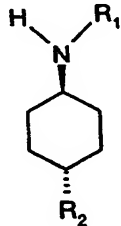


($R_2 \neq H$) exist in at least two isomeric forms:



cis

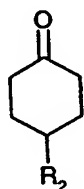
and



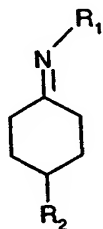
trans

In another, non-symmetrical substitution at the cyclohexyl ring, the carbon atoms are chiral in 1- and 4-position. According to the R,S-nomenclature by *Cahn, Ingold and Prelog*, sertraline has the 1S-, 4S-configuration.

Cyclohexylamine is obtained, for example, by the following method: Reacting the ketone



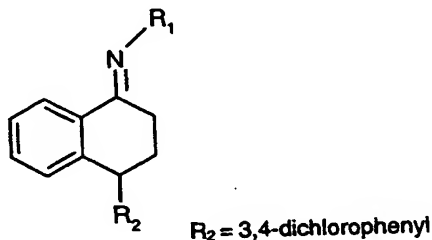
with a primary amine, e.g. methylamine, results, with elimination of water, in a cyclohexyl-imine:



The resultant imine is then catalytically hydrogenated to the amine. These reactions proceed without, or only with minor, stereoselectivity. In the case of sertraline, four enantiomers are obtained.

This invention has for its object to prepare cyclohexylamines having as high as possible a cis-isomer proportion.

To achieve this object, the above-mentioned *U.S. patent specification 4,536,518* proposes to hydrogenate an imine of formula:

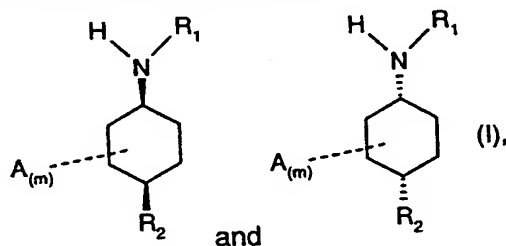


using palladium and carbon as substrates. This affords 70 % of cis- and 30 % of trans-racemate.

To further improve this yield, *WO 93/01161* proposes to replace palladium and carbon as substrate by Raney nickel when hydrogenating the imine. This results in a cis/trans ratio of 8:1. Surprisingly, it has now been found that an even better cis/trans ratio is obtained if the

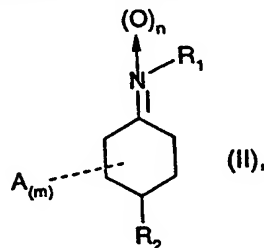
imine is catalytically hydrogenated in the presence of a copper. The preparation of secondary amines from ketones and intermediate imines by hydrogenation in the presence of copper chromite catalysts is known from *R. B. C. Pillai J. Mol. Catalysis* 84 (1993), 125 - 129. However, it is surprising that, starting from cyclohexylidenamines, which are also obtainable as intermediates from ketones, the hydrogenation by means of a copper-containing catalyst proceeds diastereoselectively and affords a high cis-isomer proportion (> 95%).

This invention relates to a process for the preparation of cis-compounds of formula:



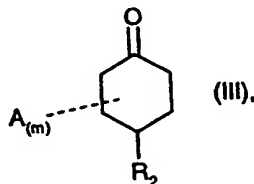
wherein R_1 and R_2 are each independently of the other hydrocarbon radicals and A is substituents, and m is an integer from 0 to 4 and defines the number of the substituents A , which process comprises

a) hydrogenating a cyclohexylidenamine of formula:



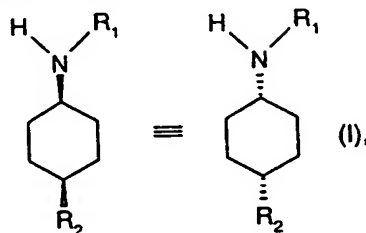
wherein n is 0 or 1 and R_1 , R_2 , A and m have the cited meanings, in the presence of a copper-containing catalyst; or

b) reacting a ketone of formula:

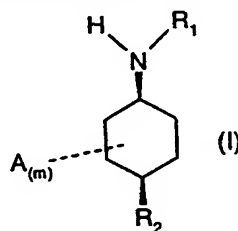


wherein R_2 , A and m have the cited meanings, with a compound introducing the $R_1-N \rightarrow (O)_n$ group, hydrogenating the imine or nitrone (II) which is obtainable as intermediate in the presence of a copper-containing catalyst and isolating the cis-compound (I).

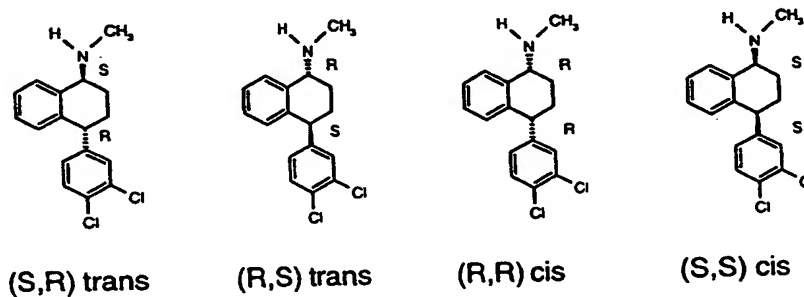
If in a compound (I) m is 0 and the cyclohexyl ring is unsubstituted, then the two structural formulae represent identical compounds:



Of the two possibilities for representing the structural formula of the cis-compound (I) in the description of this invention, only the general formula:



is used. If in a compound (I) m is 1 to 4 ($m > 0$) and the cyclohexyl ring is unsymmetrically substituted, then a cis-enantiomer pair is selectively obtained during hydrogenation which can be separated into the optically pure antipodes by customary methods of racemate resolution, for example by crystallisation of the mandelic acid salt by the method of *W.M. Welch et al in J. Med. Chem. 1984, 27, 1508-1515*. The relationship between the two cis- and trans-enantiomer pairs and the 4 optically pure antipodes is illustrated by the following formula scheme of sertraline:



In the structural formulae of the starting materials (II) and (III), the unbroken bonding dashes to the substituent R_2 signify that in the case of $R_2 \neq H$ and of different substitution at the cyclohexyl ring, these starting materials can be used in the process in the form of racemic mixtures having identical or different antipode proportions or in the form of an optically pure antipode.

The process is distinguished by a high yield of the desired cis-compounds. In the case of the synthesis of sertraline, a ratio of the cis- to the trans-enantiomer pair is obtained which is higher than 95:5. In a particularly preferred embodiment of this invention, the even better ratio of higher than 99:1 is obtained. This high cis-compound yield obviates the separation of the cis- from the trans-enantiomer pair which is otherwise necessary when different substituents A ($m > 0$) are present.

The definitions and denotations used within the scope of the description of this invention preferably have the following meanings:

A hydrocarbon radical R_1 or R_2 is preferably selected from the group consisting of C_1 - C_{20} -alkyl, C_4 - C_{12} cycloalkyl, C_2 - C_{11} heterocycloalkyl, carbocyclic C_5 - C_{16} aryl, C_2 - C_{15} heteroaryl, carbocyclic C_7 - C_{16} aralkyl and C_2 - C_{15} heteroarylalkyl and can in addition be substituted by suitable functional groups, for example by the functional groups or derivatised functional groups consisting of amino, C_1 - C_4 alkylamino, C_1 - C_4 dialkylamino, hydroxy, carboxy and halogen.

The cyclohexyl ring can be substituted by 1 to 4, preferably by 2, substituents from the group A containing the substituents R_3 , R_4 , R_5 and R_6 . Suitable substituents are listed in the *List of Radical Names*, valid according to *IUPAC Rules*, and remain unchanged under the conditions of the catalytic hydrogenation reaction. Any of the substituents may be chosen. Suitable substituents A from the group R_3 , R_4 , R_5 and R_6 are selected, for example, from the group of the functional groups or derivatised functional groups consisting of amino, C_1 - C_4 alkylamino, C_1 - C_4 dialkylamino, hydroxy, carboxy and halogen, or are saturated or unsaturated aliphatic, cycloaliphatic or heterocycloaliphatic radicals, carbocyclic or heterocyclic aryl radicals, condensed carbocyclic, heterocyclic or carbocyclic-heterocyclic radicals, which can in turn be combined with any others of these radicals and which can be substituted by the cited functional groups or derivatised functional groups.

The cited substituents and radicals can furthermore be interrupted by one or more than one bivalent radical from the group consisting of $-O-$, $-C(=O)-O-$, $-O-C(=O)-$, $-C(=O)-N(C_1-C_4alkyl)-$, $-N(C_1-C_4alkyl)-C(=O)-$, $-S(=O)_2-$, $-S(=O)_2-O-$, $-O-S(=O)_2-$, $-S(=O)_2-N(C_1-C_4alkyl)-$, $-(C_1-C_4alkyl)N-S(=O)_2-$, $-P(=O)-$, $-P(=O)-O-$, $-O-P(=O)-$ and $-O-P(=O)-O-$.

In a preferred embodiment of this invention, two substituents A from the group R_3 , R_4 , R_5 and R_6 are bivalent, bridge-like C_2 - C_6 alkylene, C_4 - C_8 alkyldiylidene or C_4 - C_8 alkenyldiylidene groups, preferably butanediylidene, more preferably 2-butenediylidene, which is bound with the cyclohexyl ring to two adjacent carbon atoms and which forms together with these car-

bon atoms a phenyl ring which can be substituted by the cited functional groups or substituents.

Suitable substituents A from the group R₃, R₄, R₅ and R₆ are also substituents from the group C₁-C₂₀alkyl, C₄-C₁₂cycloalkyl, C₇-C₁₂bicycloalkyl, C₂-C₁₁heterocycloalkyl, carbocyclic C₆-C₁₆aryl, C₂-C₁₅heteroaryl, carbocyclic C₇-C₁₆aralkyl and C₂-C₁₅heteroarylalkyl, which can in turn be substituted by the cited functional groups and interrupted by bivalent radicals.

C₁-C₂₀Alkyl is, for example, methyl, ethyl, n- or isopropyl or n-, sec- or tert-butyl and straight-chain or branched pentyl, hexyl, heptyl, octyl, isooctyl, nonyl, tert-nonyl, decyl, undecyl or dodecyl.

C₄-C₁₂Cycloalkyl is, for example, cyclopropyl, dimethylcyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

C₇-C₁₂Bicycloalkyl is, for example, bornyl or norbornyl.

C₂-C₁₁Heterocycloalkyl preferably contains 4 or 5 carbon atoms and one or two heteroatoms from the group O, S and N. Examples are the substituents derived from oxirane, azirine, 1,2-oxathiolane, pyrazoline, pyrrolidine, piperidine, piperazine, morpholine, tetrahydrofuran or tetrahydrothiophene.

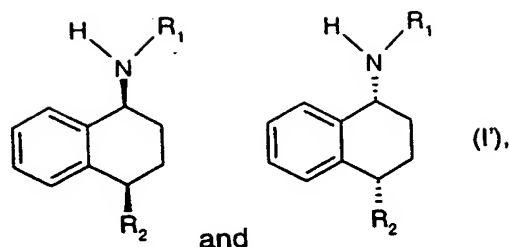
Carbocyclic C₆-C₁₆aryl is, for example, mono-, bi- or tricyclic, typically phenyl, naphthyl, indenyl, azulenyl or anthryl.

C₁-C₁₅Heteroaryl is preferably monocyclic or is condensed with a further heterocycle or with an aryl radical, for example phenyl, and preferably contains one or two, in the case of nitrogen up to four, heteroatoms from the group O, S and N. Suitable substituents are derived from furan, thiophene, pyrrole, pyridine, bipyridine, picoline, γ -pyran, γ -thiopyran, phenanthroline, pyrimidine, bipyrimidine, pyrazine, indole, coumarone, thionaphthene, carbazole, dibenzofuran, dibenzothiophene, pyrazole, imidazole, benzimidazole, oxazole, thiazole, dithiazole, isoxazole, isothiazole, quinoline, isoquinoline, acridine, chromene, phenazine, phenoxazine, phenothiazine, triazine, thianthrene, purine or tetrazole.

Carbocyclic C₇-C₁₆aralkyl preferably contains 7 to 12 carbon atoms, e.g. benzyl, 1- or 2-phenethyl or cinnamyl.

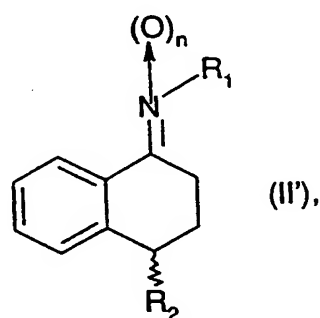
C₂-C₁₅Heteroarylalkyl preferably consists of the cited heterocycles, which substitute e.g. C₁-C₄alkyl radicals, depending on the length of the carbon chain where possible terminally, or else also in adjacent position (1-position) or in α -position (2-position).

In a preferred embodiment of this invention, a cis-enantiomer pair of the compound of formulae:



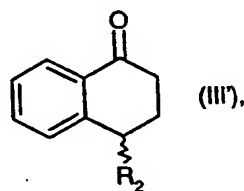
is prepared, wherein R_1 is C_1 - C_4 alkyl and R_2 is aryl.

According to process variant a) a cyclohexylidenamine, or the imine or nitron (II), preferably the imine or nitron of formula:



wherein R_1 and R_2 have the cited meanings, which imine or ketone may be in syn- or anti-form, is hydrogenated in the presence of a copper-containing catalyst.

According to process variant b) a ketone (III), preferably a ketone of formula



wherein R_2 has the cited meanings, is reacted with a compound introducing the $R_1-N \rightarrow (O)_n$ group, in particular with a primary amine, preferably methylamine, or with a R_1 -substituted hydroxylamine, preferably N-methylhydroxylamine, and the imine (II) which is obtainable as intermediate is hydrogenated *in situ* in the presence of a copper-containing catalyst. It is also possible to replace the racemic compound (II') or (III') with an optically pure compound (II'') or (III'') and to react it to a cis-compound (I').

This invention preferably relates to a process for the preparation of the cis-compound (I'), wherein R_1 is methyl and R_2 is 3,4-dichlorophenyl, which process comprises

a) hydrogenating an imine or nitron (II'), wherein R_1 is methyl and R_2 is 3,4-dichlorophenyl, in the presence of a copper-containing catalyst, or

b) reacting a ketone (III'), wherein R_2 is 3,4-dichlorophenyl, with methylamine or N-methyl-hydroxylamine, hydrogenating the imine or nitron (II) which is obtainable as intermediate in the presence of a copper-containing catalyst and isolating the cis-compound (I').

Suitable catalysts for the hydrogenation reaction according to variants a) and b) are copper-containing catalysts, for example copper skeleton, copper substrate, copper chromite, copper zinc oxide, copper boride or copper urushibara catalysts.

In a preferred embodiment of this process, other elements are present in the catalyst besides copper. Examples thereof are aluminium, chromium, zinc, barium, manganese, zirconium, vanadium, molybdenum, titanium, tantalum, niobium, tungsten, nickel, cobalt, bismuth, tin, antimony, hafnium, rhenium, iron, cadmium, lead or germanium and mixtures thereof. The amount in which the element is added can vary within wide limits and may be from 10 ppm to 200% in relation to the amount of copper used. Particularly suitable elements are aluminium, zinc, chromium, barium and manganese. The elements can be, for example, in the form of oxides or salts, such as chromates.

Raney copper is an example of a suitable copper skeleton catalyst.

Examples of substrates are carbon, aluminium oxide, silicon dioxide, Cr_2O_3 , zirconium dioxide, zinc oxide, calcium oxide, magnesium oxide, barium sulfate, calcium carbonate or aluminium phosphate. The copper can be bound on the substrate in an amount of about 1.0 - 20.0 % by weight.

A suitable copper chromite catalyst is represented by the empirical formula $CuO \cdot CuCr_2O_4$. $CuCr_2O_4$ is known, see *C.A.R.N. 12018-10-9* and *Gmelins Handbuch der Anorganischen Chemie, 8th ed., Vol. Kupfer, part B, instalment 3, system number 60, page 60*. A common name is also copper(II)chromate(III). Copper chromite catalysts having changing proportions of CuO and $CuCr_2O_4$, Raney copper catalysts and copper-zinc-aluminium-oxide catalysts are commercially available in pure form or in a form doped with the cited elements.

In a preferred embodiment of the process, the copper-containing catalysts used are copper chromite catalysts or catalysts containing copper, zinc and aluminium in the form of oxides.

The cited catalysts are present in the reaction mixture in an amount of about 0.1 to 100 % by weight, preferably of 1-20 % by weight, based on the amount of educt used.

The copper-containing catalysts can be used in different ways in the process:

- in the form of ready-to-use catalysts;

- in the form of prehydrogenated catalysts, or
- in the form of catalysts prepared in situ from suitable precursors, such as copper salts or oxides, and from other compounds.

For the prehydrogenation it is possible to treat e.g. a suspension of the catalyst in a suitable solvent under 5 to 150 bar hydrogen at 80-250°C for half an hour to 5 hours, or hydrogen is introduced under normal pressure up to 50 bar at 100 to 500°C over the dry catalyst.

In preferred embodiment of the process, the catalyst used is activated by hydrogenation in the solvent which is used for hydrogenating the imine or nitron (‘‘prehydrogenation’’). The catalyst can be separated after the hydrogenation e.g. by filtration if the process is carried out batchwise.

Imines (II) can be prepared by reacting ketones (II) with a compound introducing the R_1-N group, in particular with a primary amine, preferably methylamine. The preparation of imines (II) is carried out in analogy to the method which is described in *U.S. patent specification No. 4,536,518*.

Nitrones (II) can be prepared by reacting ketones (II) with a compound introducing the $R_1-N \rightarrow O$ group, for example R_1 -substituted hydroxylamine, preferably N-methylhydroxylamine. The preparation of nitrones (II) is carried out in analogy to the method described in *WO 98/27050*.

Hydrogenation is carried out in the presence of an organic solvent. It is preferred to use non-polar or polar aprotic solvents or mixtures thereof.

Examples of suitable non-polar solvents are hydrocarbons, for example aliphatic hydrocarbons, such as hexane, heptane or petroleum ether, cycloaliphatic hydrocarbons, such as cyclohexane or methylcyclohexane, aromatic hydrocarbons, such as benzene, toluene or xylene.

Examples of suitable polar aprotic solvents are ethers, such as aliphatic ethers, e.g. 1,2-diethoxyethane or tert-butylmethyl ether, cyclic ethers, e.g. tetrahydrofuran or dioxan, amides, e.g. dimethylformamide or N-methylpyrrolidone. Ethers are particularly suitable, especially tetrahydrofuran.

In accordance with variant b) acid assistants are added where required, for example organic mono- or polyvalent acids containing more than two carbon atoms, for example acetic acid, propionic acid or malonic acid, mineral acids such as sulfuric acid, so-called Lewis acids, such as boron trifluoride, or so-called solid acids, such as zeolites or Nafion® and/or dehydrating agent, such as sodium sulfate.

In accordance with variant b) an excess of up to 50 mol of the amine used is added, for example methylamine in the form of methylamine gas or as a solution, e.g. in ethanol.

The process can be carried out in both variants preferably in the liquid phase batchwise or continuously, preferably with a catalyst suspension as liquid-phase hydrogenation or in a bubble column or with a formulated catalyst in a trickle bed. The reaction can also be carried out in the gas phase with a powdered catalyst in a fluidised bed or with a formulated catalyst in a fixed bed.

The hydrogenation can be carried out in a wide range of temperatures. Temperatures in the range from 60° to about 250 °C, preferably from 90° to 150°C, have been found to be advantageous.

The hydrogen pressure can vary within a wide range during hydrogenation, for example from 1 - 100, preferably from 5 - 50, more preferably from 10 - 20 bar. Which hydrogen pressure is used depends essentially on the hydrogenation plant available. At higher temperatures of about 100°C, molecular hydrogen can also be replaced by a hydrogen-donor, such as isopropanol.

The reaction time can vary within wide limits. It depends on the catalyst used, on the hydrogen pressure, on the reaction temperature and on the plant used and can be, for example, from half an hour to 24 hours. Advantageous reaction times are those from about half an hour to 2 hours.

The isolation of the reaction products is carried out by known methods and is illustrated in the Examples. After separation of the catalyst and removal of the solvent, the conventional separation processes may follow, for example preparative thin-layer chromatography, preparative HPLC, preparative gas chromatography etc.. The cis-racemate obtained starting from racemic cyclohexylidenamine can be separated into the optically pure antipodes without any further purification using the known processes for enantiomer separation, for example by means of preparative chromatography on chiral substrates (HPLC) or by precipitation or crystallisation using optically pure precipitants, for example D -(-) or L -(-)-mandelic acid or (+) or (-)-10-camphorsulfonic acid. Starting from enantiomer-pure 4-substituted cyclohexylidenamine, the enantiomer-pure 4-substituted cyclohexylamine is obtained directly by the hydrogenation process of this invention.

This invention also relates to the use of copper-containing catalysts for the diastereoselective hydrogenation of cyclohexylidenamines. In this case it is preferred to use copper chromite catalysts or CuZnAl-oxide catalysts for the diastereoselective hydrogenation of cyclohexylidenamines.

The following Examples illustrate the invention:

Example 1 (Hydrogenation of the imine).

0.1 g of barium-doped copper chromite catalyst (commercial product of Südchemie, Girdler G 13, comprising 29% of Cu, 26% of Cr and 13.6% of Ba) and 40 ml of THF are placed in a 100 ml autoclave (stainless steel 316SS). The catalyst suspension is prehydrogenated for 1 hour at 12 bar initial pressure H_2 at 130°C. The suspension is then cooled and 0.5 g of 4-(3,4-dichlorophenyl)-1-methylimino-1,2,3,4-tetrahydronaphthalene is added. Subsequently, hydrogenation is carried out for 18 hours at 100°C and 12 bar initial pressure H_2 (maximum pressure: 15 bar). The catalyst is removed by filtration and the product is concentrated by evaporation under vacuum and dried under high vacuum. According to 1H -NMR spectrum, the cis/trans ratio of the resulting 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthylamine is > 95 : 5. The crude product is purified via FLASH chromatography over silica gel at a solvent gradient of CH_2Cl_2 to $CH_2Cl_2/MeOH$ (9 : 1). This gives 83 % of the theoretical yield of pure cis-racemate.

Example 2 (Reductive alkylation)

1.0 g of 4-(3,4-dichlorophenyl)-1-oxo-1,2,3,4-tetrahydronaphthalene and 0.2 g of barium-doped copper chromite catalyst (see Example 1) are placed in 40 ml of THF in a 100 ml autoclave (stainless steel 316SS). Subsequently, 2.25 ml of methylamine solution in ethanol (14.2% G/V) are added by means of a syringe. 120 bar of hydrogen are then forced in and hydrogenation is carried out for 16 hours at 110°C and for 18 hours at 130°C. The catalyst is removed by filtration and the product is concentrated by evaporation under vacuum and dried under high vacuum. According to 1H -NMR spectrum, the cis/trans ratio of the resultant 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthylamine is > 9 : 1. The crude product is purified via FLASH chromatography over silica gel at a solvent gradient of CH_2Cl_2 to $CH_2Cl_2/MeOH$ (9 : 1). This gives 50 % of the theoretical yield of pure cis-racemate.

Example 3 (Hydrogenation of the imine).

0.4 g of catalyst (commercial product of Engelhard, Cu-0890 P, comprising 35% of CuO , 42% of ZnO and 21% of Al_2O_3) and 80 ml of THF are placed in a 300 ml autoclave (stainless steel 316SS). The catalyst suspension is prehydrogenated for 2 hours at 10 bar initial pressure H_2 at 150°C. The suspension is then cooled and 2 g of 4-(3,4-dichlorophenyl)-1-methylimino-1,2,3,4-tetrahydronaphthalene are added. Subsequently, hydrogenation is carried out for 30 minutes at 100°C and at 10 bar initial pressure H_2 (maximum pressure: 15 bar). The catalyst is removed by filtration (over Hyflo®) and 0.5ml of the solution are concentrated by evaporation under vacuum. The sample is taken up in isopropanol and the cis/trans ratio of

the resultant 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthylamine is determined via HPLC: 97.3 to 2.7. 20ml of a HCl-saturated THF solution are then added dropwise at 0°C to the solution of crude product. The corresponding crystalline hydrochloride precipitates and is collected by filtration over a glass suction filter and dried under vacuum. This gives 85% of the theoretical yield of pure cis-racemate. The melting point is 292-293°C after recrystallisation from absolute methanol.

Example 4 (Hydrogenation of the imine, without prehydrogenation of the catalyst).

0.06 g of catalyst (commercial product of Engelhard Cu-0890 P, comprising 35% of CuO, 42% of ZnO and 21% of Al₂O₃), 30 ml of THF and 3 g of 4-(3,4-dichlorophenyl)-1-methyl-imino-1,2,3,4-tetrahydronaphthalene are placed in a 100 ml autoclave (stainless steel 316SS). Hydrogenation is then carried out for 1½ hours at 150°C and at 10 bar initial pressure H₂ (maximum pressure: 15 bar). The catalyst is removed by filtration over Hyflo® and 0.1 ml of the solution is concentrated by evaporation under vacuum. The sample is taken up in isopropanol and the cis/trans ratio of the resultant 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthylamine is determined via HPLC: 99.0 : 1.0. Subsequently, 1.5 g of D-(-)-mandelic acid are added to the solution of crude product and the solvent is stripped off, with heating, in a rotary evaporator. After drying for 12 hours under high vacuum, 100 ml of ethanol are added and the corresponding crystalline mandelate is dissolved under reflux conditions. After heating for 20 minutes the solution is cooled and stored overnight at room temperature. The colourless crystals are filtered over a glass suction filter and the mother liquor is concentrated to half its volume and, after brief heating, cooled to the second crystallisation. This gives a further product fraction. The total yield is 82% of theory. The melting points are 191°C and 190°C for the first and second fraction, respectively.

Example 5 (Hydrogenation of the nitron, with prehydrogenation of the catalyst).

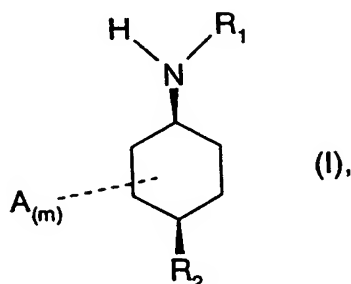
428 mg of catalyst (commercial product of Engelhard Cu-0890 P) and 35 ml of THF are placed in a 100 ml autoclave (stainless steel 316SS). The catalyst suspension is prehydrogenated for 2 hours at 12 bar initial pressure H₂ at 150°C. The suspension is cooled and then 3.01 g (9.4 mmol) of 4-(3,4-dichlorophenyl)-1-methyloxidoimino-1,2,3,4-tetrahydronaphthalene are added. Hydrogenation is then carried out for 90 minutes at 130°C and at 12 bar initial pressure H₂. The catalyst is removed by filtration and the product is concentrated by evaporation under vacuum and dried under high vacuum. The cis/trans ratio of the resultant 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthylamine according to HPLC is > 98.5 in favour of the cis-compound.

Example 6

In analogy to Example 3, 4-(3,4-dichlorophenyl)-1-methylimino-1,2,3,4-tetrahydronaphthalene is hydrogenated using the catalysts X 572P (Engelhard, CuO, CaSiO_x, C), X 540 P (Engelhard CuO, AlO_x, MnO₂) and Cu1890P (Engelhard CuCrO_x, 42% Cu, 31% Cr). The cis/trans ratio according to HPLC is 98.0 (X572P), 98.3 (X540P) and 99.2 (Cu1890P) in favour of the cis-compound.

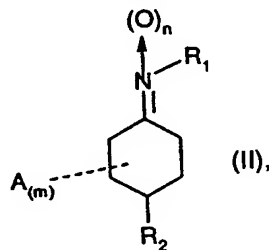
What is claimed is

1. A process for the preparation of a compound of formula



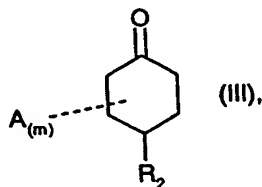
wherein R_1 and R_2 are each independently of the other hydrocarbon radicals and A is substituents, and m is an integer from 0 to 4 and defines the number of the substituents A , which process comprises

- a) hydrogenating a cyclohexylenimine of formula:



wherein n is 0 or 1 and R_1 , R_2 , A and m have the cited meanings, in the presence of a copper-containing catalyst; or

- b) reacting a ketone of formula:



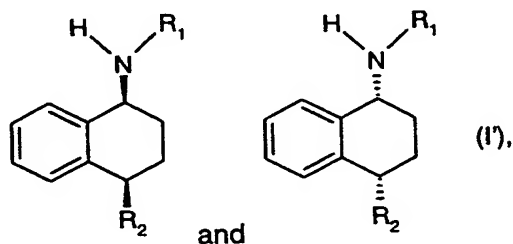
wherein R_2 , A and m have the cited meanings, with a compound introducing the $R_1-N \rightarrow (O)_n$ group, hydrogenating the imine or nitrone (II) which is obtainable as intermediate in the presence of a copper-containing catalyst and isolating the cis-compound (I).

2. A process for the preparation of a compound of formula I, wherein the hydrocarbon radicals R_1 or R_2 are selected from the group consisting of C_1 - C_{20} alkyl, C_4 - C_{12} cycloalkyl, C_4 - C_{12} cycloalkenyl, C_2 - C_{11} heterocycloalkyl, carbocyclic C_6 - C_{16} aryl, C_2 - C_{15} heteroaryl, carbocyclic C_7 - C_{16} aralkyl and C_2 - C_{15} heteroarylalkyl and are substituted by functional groups

from the group consisting of amino, C₁-C₄alkylamino, C₁-C₄dialkylamino, hydroxy, carboxy and halogen, m is 2 and A is the substituents R₃ and R₄ which are each independently of one another or in combination saturated aliphatic, cycloaliphatic or heterocycloaliphatic radicals or carbocyclic, heterocyclic or carbocyclic-heterocyclic radicals which may be combined with any others of these radicals and which may be substituted by functional groups from the group consisting of amino, C₁-C₄alkylamino, C₁-C₄dialkylamino, hydroxy, carboxy and halogen, which process comprises

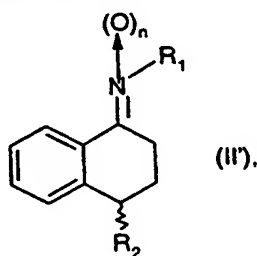
- a) carrying out the process variant a) with a corresponding substituted imine (II), wherein m is 2 and R₁, R₂, R₃ and R₄ have the cited meanings, or
- b) carrying out the process variant b) with a corresponding substituted ketone (II), wherein m is 2 and R₃ and R₄ has the cited meanings.

3. A process according to either claim 1 or claim 2 for the preparation of the cis-enantiomer pair of the compound of formula



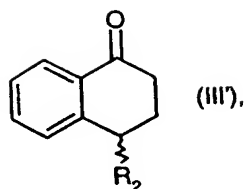
wherein R₁ is C₁-C₄alkyl and R₂ is aryl, which process comprises

- a) hydrogenating an imine or nitrone of formula



wherein R₁ is methyl and R₂ is 3,4-dichlorophenyl, in the presence of a copper-containing catalyst; or

- b) reacting a ketone of formula



wherein R₂ has the cited meanings, with a compound introducing the R₁-N group, hydrogenating in situ the imine or nitron (II) which is obtainable as intermediate in the presence of a copper-containing catalyst and isolating the compound (I').

4. A process according to claim 3 for the preparation of the cis-compound (I'), wherein R₁ is methyl and R₂ is 3,4-dichlorophenyl, which comprises
 - a) hydrogenating an imine or nitron (II'), wherein R₁ is methyl and R₂ is 3,4-dichlorophenyl, in the presence of a copper-containing catalyst, or
 - b) reacting a ketone (III'), wherein R₂ is 3,4-dichlorophenyl, with methylamine or N-methylhydroxylamine, hydrogenating the imine or nitron (II) which is obtainable as intermediate in the presence of a copper-containing catalyst and isolating the cis-compound (I').
5. A process according to any one of claims 1 to 4, which comprises preparing the compound (I) by hydrogenation in the presence of a copper chromite or CuZnAl-oxide catalyst.
6. Use of a copper-containing catalyst for the cis-selective hydrogenation of cyclic imines.
7. Use according to claim 6 of a copper chromite catalyst or CuZnAl-oxide catalyst as a catalyst for the cis-selective hydrogenation of cyclohexylidenamines.

INTERNATIONAL SEARCH REPORT

Inter. Appl. Application No

PCT/EP 99/01696

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C209/52

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 536 518 A (WILLARD M. WELCH JR. ET AL.) 20 August 1985 (1985-08-20) cited in the application column 3, line 56 - column 4, line 23; examples 1-3	1,6
A	WO 93 01161 A (PFIZER) 21 January 1993 (1993-01-21) cited in the application page 9, line 1 - page 10, line 10	1,6

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

15 July 1999

Date of mailing of the international search report

26/07/1999

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Zervas, B

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/01696

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4536518 A	20-08-1985	AT 2668 T	15-03-1986
		AU 517357 B	23-07-1981
		AU 6389780 A	07-05-1981
		BG 60333 B	27-05-1994
		CA 1130815 A	31-08-1982
		CS 9103542 A	16-12-1992
		CS 238609 B	16-12-1985
		CS 238617 B	16-12-1985
		CS 238618 B	16-12-1985
		DD 155615 A	23-06-1982
		DD 203045 A	12-10-1983
		DK 395280 A,B,	02-05-1981
		EG 15527 A	30-04-1987
		EP 0030081 A	10-06-1981
		FI 803398 A,B,	02-05-1981
		GR 70781 A	23-03-1983
		HK 82284 A	09-11-1984
		HR 930199 B	29-02-1996
		HR 931527 B	30-04-1996
		IE 50395 B	16-04-1986
		IN 159644 A	30-05-1987
		IN 159643 A	30-05-1987
		JP 1287061 C	31-10-1985
		JP 56086137 A	13-07-1981
		JP 60005584 B	12-02-1985
		LU 88330 A	04-05-1994
		LV 5456 A	10-03-1994
		LV 5457 A	10-03-1994
		MY 32685 A	31-12-1985
		NZ 195407 A	31-05-1984
		PH 17319 A	20-07-1984
		PT 72004 A,B	01-11-1980
		SI 8012798 A	31-12-1994
		SI 8310672 A	30-04-1996
		SU 1014467 A	23-04-1983
		SU 1034602 A	07-08-1983
		YU 67283 A	31-10-1983
		YU 279880 A	30-09-1983
		ZA 8006726 A	28-10-1981
WO 9301161 A	21-01-1993	AT 132848 T	15-01-1996
		CA 2109818 A	12-01-1993
		DE 69207601 D	22-02-1996
		DE 69207601 T	23-05-1996
		DK 595851 T	12-02-1996
		EP 0595851 A	11-05-1994
		ES 2082481 T	16-03-1996
		FI 940105 A	10-01-1994
		GR 3019122 T	31-05-1996
		IE 71029 B	15-01-1997
		JP 2563754 B	18-12-1996
		JP 6509079 T	13-10-1994
		PT 100673 A	30-09-1993
		US 5442116 A	15-08-1995

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☒ FADED TEXT OR DRAWING
- ☒ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☒ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.